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EXAMINER	
MANNE, JAYANTHI	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 11/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/787,098	JORDAN ET AL.	
	Examiner	Art Unit	
	Jayanthi Manne	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-14 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-14 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 1-13 and 14 are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 20040227 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 20040518.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C.121:

I. Claims 1-6, 10 and 11, drawn to a congenic rat comprising GPR10 a mutant gene; a tissue or cell; a culture of the cell; a method to screen for a compound that inhibits GPR10 protein activity, classified in class 800, subclass 13; class 435, subclass 353.

II. Claims 7 and 8, drawn to a DNA sequence encoding of SEQ ID No:7 or SEQ ID NO:9; and the DNA sequences encoding of SEQ ID NO:2 or SEQ ID NO:5, classified in class 536, subclass 23.5.

III. Claim 9, drawn to isolated fragment of human GPR10 consisting of the amino acid sequence of SEQ ID NO:10, classified in class 530, subclass 350.

IV. Claims 12 and 13, drawn to a screening assay for a compound that inhibits GPR10 protein activity and release of arachidonic acid metabolite, comprising use of tissue or cells, classified in class 435, subclass 352.

V. Claim 14, drawn to a screening assay and administering the compound useful in treating depression or anxiety, classified in class 424, subclass 9.1.

The inventions are distinct, each from other because of the following reasons:

1. Inventions I and II are patentably distinct because the inventions are drawn to distinct compositions. Inventions I and II are related as combinations and

subcombination. Inventions in this relationship are distinct if it can be shown that (1) the combination as claimed does not require the particulars of the subcombination as claimed for patentability, and (2) that the subcombination has utility by itself or in other combinations (MPEP § 806.05(c)). The subcombination in Group II, which is the DNA molecule, has separate utility because it can be used to transfect cells. Thus, the inventions of Groups I and II are drawn mutually exclusive compositions that are patentably distinct, each from the other.

2. Inventions I and III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together (MPEP § 806.04, MPEP § 808.01). In the instant case the invention in Group I is drawn to a congenic rat comprising mutant GPR10 gene and a method to screen a compound that inhibits GPR10 protein activity. The invention in Group III is drawn to human GPR10 protein that is structurally, chemically, biologically and functionally different from the animal in the invention of Group I. The invention of Group III is a isolated fragment of human GPR10 protein, which comprises amino acids, which is structurally different from animal in the invention of Group I which consists of tissues and cells that have specialized functions.

3. Inventions I and IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the

process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). The cells of the invention of Group I can be used in the method of the invention of Group IV. In this case, the cells can also be used to produce the mutant GPR10 protein in culture.

4. Inventions I and V are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the invention in Group V can be used in administering the compound in any mammal for example a mouse suffering from depression or anxiety. The animal of the invention in Group I is not required in the method, because the invention of the Group V is drawn to in vivo assay that is administering the test compound that inhibits GPR10 protein to any mammal suffering from depression or anxiety.

5. Inventions II and III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together (MPEP § 806.04, MPEP § 808.01). In the instant case the invention in Group II is drawn to a DNA molecule and invention in Group III is drawn to human GPR10 protein that are different.

The DNA molecule is a polynucleotide; and the protein of the invention of Group III is composed of amino acids that are structurally, functionally, biologically and chemically distinct molecules.

6. Inventions II and IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together (MPEP § 806.04, MPEP § 808.01). In the instant case the invention in Group II is drawn to a DNA molecule and the invention in Group IV is the method drawn to screening assay for the compound that inhibits GPR10 protein activity. In this case the DNA cannot be used in the method. Furthermore, the invention in Group IV is the method; and the method is using cells in screening a compound that inhibits GPR10 protein activity.

7. Inventions II and V are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together (MPEP § 806.04, MPEP § 808.01). In the instant case the invention in Group II is drawn to a DNA molecule; the invention in Group V is drawn to a method using an animal, not DNA; and in this case, the DNA molecule of the invention in Group II cannot be used in the invention of Group V the claimed method to screening and administering a compound in treating depression or anxiety.

8. Inventions III and IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the invention in Group III is a drawn to a human GPR10 protein and the invention of Group IV is drawn to a screening assay for a compound that inhibits GPR10 protein activity. The invention in Group IV is a method and the method is use with protein or cells in screening assay for compound that inhibits GPR10 protein activity. The process for using the protein as claimed can be practiced with another materially different product. For example, the method can be practiced with the cells. The protein can be used in a materially different process of using the protein. For example, the protein can be used in a binding assay.

9. Inventions III and V are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together (MPEP § 806.04, MPEP § 808.01). In the instant case the invention in Group III is drawn to isolated human GPR10 fragment, whereas the invention in Group V is drawn to screening of compound in treating disease in a mammal and does not require use of protein. The protein in the invention in Group III cannot be used in the method in invention in Group V.

10. Inventions IV and V are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together (MPEP § 806.04, MPEP § 808.01). In the instant case the invention in Group IV and V are unrelated because the invention in Group IV is drawn to a method of screen a compound that results in determining the action of the compound on GPR10 protein activity, whereas the invention in Group V is drawn to a screening assay and administering said compound to a mammal in treating depression or anxiety. The method in the invention in Group IV is drawn to in vitro assay that requires a cell or tissue to study the compound that inhibits GPR10 protein activity, whereas the invention in Group V is drawn to in vivo assay that requires administering the compound in any mammal suffering from depression or anxiety.

During a telephone conversation with Gordon Kit on 9/15/2004 a provisional election was made to prosecute the invention of Group I, claims 1-6, 10 and 11. Affirmation of this election must be made by applicant in replying to this Office action. Claims 7-9 and 12-14 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or

otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to the final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain

dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and recognized divergent subject matter and because the searches the required for the separate inventions are not coextensive, restriction for examination purposes as indicated is proper.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer as inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

DETAILED ACTION

Claims 1-14 are pending in the instant application.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-6, 10 and 11 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility.

Claims 1-6 are directed to a congenic rat comprising a mutant GPR10 gene.

Claim 10 is directed to a method for screening for a compound that inhibits GPR10 protein activity.

Claim 11 is directed to method relating GPR10 activity to depression in a forced swimming test or fear and anxiety in an elevated plus-maze test.

Utility Guidelines: See the Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pp. 1092-1099 (January 5, 2001).

A **credible** utility is one that a person of ordinary skill in the art would accept as currently available. An assertion is considered credible unless (a) the logic underlying the assertion is seriously flawed, or (b) the facts upon which the

assertion is based are inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the Applicant to support the assertion of utility. A credible utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use.

A **specific** utility is one that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention.

A **substantial** utility is one that defines a real world use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a real world context of use are not substantial utilities. Research that involves studying the properties of the claimed product itself does not constitute a substantial utility.

Asserted Utilities: The specification asserts that the claimed congenic rat can be used as a model for treating psychiatric diseases such as depression or anxiety (page 1, line 10-11). The specification asserts that the congenic rat claimed in the invention is believed to be useful in behavioral tests, because of the avoidance of the body weight difference against the control rat (page 8, lines 15-

18). The specification also asserts that by comparing the congenic rat of the present invention (or their tissues or cells) to wild-type rats (or their tissues or cells), it is possible to screen for the biological functions of GPR10, and to screen for compounds that inhibit GPR10 protein activity (page 28, lines 24-28). The specification also asserts that the biochemical, physiological and behavioral differences between rats from the same species expressing wild-type and truncated GPR10 are useful tools for identifying novel functional roles for GPR10 and the potential pathological relevance of GPR10 to human diseases (page 3, lines 27-32).

Teachings of the Specification: The specification disclose the physiological relevance of the NH2-terminus by comparing rats expressing wild-type and mutant forms of GPR10, the rats expressing mutant form of GPR10 were found to display depressed-like and less anxious-like behaviors in animal models commonly used to predict anti-depressant and anxiolytic drug activity (page 4, lines 14-20). The specification also discloses congenic generation as N5 generation, the background genome of these rats had already been replaced by 97 to 99% of the BN genome. Heterozygous rats were selected and subsequently intercrossed to establish the homozygous congenic rat (page 46, lines 9-14). The specification discloses the selection of congenic rat produced comprising the mutant GPR10 gene and conducting the behavioral tests (page 8, lines 18-20). The specification discloses the results of a forced swimming test using congenic

rat expressing mutant GPR10 (figure 13 on page 47) indicating increase in immobile time comparing to that of control+/+ rats and suggesting the immobility to a state of lowered mood or hopeless. The specification discloses the elevated plus-maze test to determine possible interfering emotional factors in congenic expressing mutant GPR10 (Page 48, lines 24-25), the congenic rats showed a prolonged time spent in the open arms and a shorter time spent in the closed arms compared to wild-type rats and total moving distance was longer in the congenic rats than the wild-type rats (Page 49, lines 13-22). Examples 6-10 disclose use of human wild-type GPR10 and mutant GPR10 gene. The specification states the effect of PrRP and compound X on PrRP binding to CHO cells stably expressing cloned human wild-type and mutant GPR10 (example 6, figure 14 and 15) indicating a direct evidence that the 125 I PrRP binding site resides within the first 64 amino acids of the NH2-terminus of the human GPR10 receptor, and this binding site consists of two binding domains that contact 125I PrRP each at a subnanomolar binding affinity. The specification further in Figures 16-17, (Page 53, lines 28-30) states increasing concentrations of PrRP competitively displaced 125 I PrRP binding to CHO-hGPR10 cell membrane. The specification states in example 8 the effects of PrRP and Compound X on 3H-arachidonic acid release from CHO cells stably expressing cloned human mutant GPR10 and assay revealed that PrRP was inactive (figure 19, page 58, line 6) and compound X activate CHO-hGPR10 cells by respective activation at an orthosteric and allosteric site located at different positions within the cloned human GPR10

receptor (example 8). The specification further states synergistic effect of compound X on PrRP stimulated 3H arachidonic acid release from CHO cells stably expressing cloned human mutant GPR10 indicating that PrRP has the capacity to enhance the activity of compound X (example 10, page 63, lines 1-2).

The various asserted utilities are addressed in turn as follows:

(1) The specification discloses that congenic rat of the invention can be used as model for treating psychiatric diseases such as depression (page 1, line 10-11). While this utility is specific to the congenic mutant rat of the invention, it is not a credible utility as a model for human disease. The reason this is not a credible utility is because human depression has not been linked to mutations in GPR10. In humans, mutation in GPR10 gene has been reported. Bhattacharyya et al (2003, Diabetes 52:1296-1299) disclosed in his study conducted in U.K. Caucasian population that mutation in GPR10 gene is associated with blood pressure and not obesity. Two genetic variants V283I and P305L were detected at the GPR10 locus. Individuals with allelic variant P305L showed a significantly lower systolic and diastolic blood pressure compared to individuals with wild-type providing a functional basis for this association.

The prior art discloses GPR10 is a novel G-protein coupled receptor that is the human orthologue of Unknown Hypothalamic Receptor-1 (UHR-1) and Prolactin-releasing peptide (PrRP) is an endogenous ligand for GPR10 that binds to activate the GPR10 receptor (Langmead et al, Br J Pharmacol 131:683-688, 2000; Barbara et al, Endocrinology 140:5736-5745, 1999). The role of GPR10 in regulation of food intake

and body weight was disclosed by Gu et al (J Mol Neurosci, 22: 93-103, 2003) by generating transgenic mice carrying a targeted deletion of the GPR10 gene. Using knockout mice it was confirmed first, that GPR10 is the principle receptor for PrRP in the mouse hypothalamus, because deletion of GPR10 completely abolished PrRP binding to isolated hypothalamic cell membranes. The GPR10 knockout mice at 16 weeks of age on a normal diet became hyperphagic, obese and showed significant increases in body fat compared to high-fat diet on wild-type mice providing a direct evidence that GPR10 is the receptor for PrRP and that it is involved in the regulation of energy balance in mice.

Taken together in humans, mice and rats the mutations in GPR10 gene have disclosed different phenotypes. In human the mutation in GPR10 gene is associated with blood pressure and not obesity. The deletion of GPR10 gene in knockout mice showed an increase in body weight, body fat and levels of leptin and insulin and decreased glucose tolerance. The mutation in GPR10 in the claimed congenic rat showed increase in immobilization and anti-anxiety like condition. Congenic rat claimed in the invention cannot be used as a model for human depression or anti-anxiety, because the observed phenotypes clearly vary among species and therefore are not representative of the effect of GPR10 mutations in humans. Thus, the congenic rat is not a model of human disease.

(2) Useful in behavioral tests comparing to control rat. The congenic mutant rat exhibited a prolonged immobilization time when assayed in a forced swimming test and anti-anxiety behavior in an elevated plus-maze test compared to wild-type rat (page 7, lines 14-18). This asserted utility is credible however this credible utility is not a

substantial or specific utility. Thus, this credible utility is not a real world utility. It constitutes studying the product made, i.e. the rat. The congenic rat exhibiting anti-anxiety behavior is not a phenotype that can correlate to disease, because anti-anxiety is not a disease, and anti-anxiety phenotype cannot be used in human depression.

(3) Using the congenic rats to screen for the biological functions of GPR10 protein activity and to screen for compounds that inhibit GPR10 activity. This asserted utility is credible. But this is not a substantial utility. Using the claimed congenic rat to study the protein is not a real world utility since it constitutes further research to identify or reasonably confirm a real world utility.

(4) The biochemical, physiological and behavioral differences between rats from the same species expressing wild-type and truncated GPR10 are useful tools for identifying novel functional roles for GPR10 and potential pathological relevance of GPR10 to human disease (page 3, lines 27-32). This asserted utility is a credible utility. While this utility is specific to congenic rat of the invention, it is not a substantial utility because it is not a real world utility. The asserted utility is not a real world utility because it constitutes further research to identify or reasonably confirm a real world utility.

The specification discloses that the congenic rat of the invention exhibit significant depression (Figure 13, Page 49, lines 33-34), but fails to disclose any

correlation to humans with depression or to humans with GPR10 mutation. Thus, congenic rat is not a model for human depression.

Taken as a whole, the congenic mutant rat is not a representative of animal model for depression in humans.

Furthermore, neither the prior art nor the instant specification, discloses that the mutant GPR10 gene is associated with human depression and anti-anxiety. Further research would be required to identify such an association in humans, if any.

For the reasons discussed above, the results presented in the instant specification do not indicate that the invention can be used in modeling human depression.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 10 and 11 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Enablement

Claims 1-6, 10 and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, are set forth in *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988). These factors include: (1) the nature of the invention, (2) the state of the prior art, (3) the relative level of skill of those in the art, (4) the predictability of the art, (5) the breadth of the claims, (6) the amount of direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary (MPEP 2164.01(a)).

Nature of the invention and breadth of the claims. Claim 1 is directed to a congenic rat comprising a GPR10 mutant gene obtained by crossing OTELF rat (ATCC No. 72016) with a wild-type rat exhibits a prolonged immobilization time in a forced swimming test and anti-anxiety behaviour in an elevated plus-maze test compared to the control rat wild-type rat. Claim 2 is directed to congenic rat comprising mutant GPR10 with DNA sequence of SEQ ID NO:2. Claim 3 is directed to congenic rat comprising wild-type GPR10 with DNA sequence of SEQ ID NO:1. Claim 4 is directed to congenic OTELF rat comprising mutant GPR10 gene. Claim 5 is directed to a tissue or cell

obtained from congenic rat expressing GPR10 gene. Claim 6 is directed to a culture of the cell obtained from congenic rat comprising GPR10 mutant gene. Claim 10 is directed to a method of screening for a compound that inhibits GPR10 protein activity. Claim 11 is directed to a method relating GPR10 activity to depression in a forced swimming test or fear and anxiety in an elevated plus-maze test.

Amount of direction or guidance presented and presence or absence of working examples.

The teachings of the specification are discussed in detail above.

State of the prior art and level of predictability in the art

A congenic strain is one that is genetically identical to a control strain except for a single chromosomal region and any physiological differences between the congenic strain and the control strain can be attributed to genes in the congenic donor region. Although the generation of congenic mice is simple; atleast six generations of backcross breeding is required before the genetic backgrounds are statistically >99% homogenous, and the return on additional generations of backcross breeding markedly diminishes thereafter. For example, it requires 4 additional generations to increase genetic homogeneity from 92.2% to 99.95% (Sigmund, page 1427, column 1, paragraph 1and 2; Arterioscler Thromb vasc Biol 20: 1425-1429, 2000). Genetically engineered mice are not always useful because they frequently do not yield the expected phenotype, or they don't seem to have any phenotype (Doetschman, page 137, column 1, paragraph 1; Laboratory Animal

Science 49: 137-143, 1999). Phenotypic effects of a knockout mice often depend on the genetic background of the mouse strain carrying the mutation, but the effects of environmental background are not generally known (Crabbe et al, page 1670, column 1, Science 284:1999). On the other hand the generation of congenic strains also provides an opportunity to place the target locus on a number of different genetic backgrounds and thus directly test for strain-specific modifier loci (Sigmund 2000, page 1427, paragraph 1, column 1; Arterioscler Thromb vasc Biol 20: 1425-1429). While many congenic strains have been produced that retain phenotypes for complex traits, it is always possible that a new congenic strain will not exhibit a target phenotype. The most likely reasons are that the original quantitative trait loci (QTL) might have been a false positive or the original QTL might have been dependent on interaction with other donor strain genes that would be lost during the construction of congenic strains. Retention of phenotypes by congenic strains is the critical test of whether or not they will be useful for isolation of the underlying gene (Diament et al, 2004, page 452, column 2, paragraph 2; Mammalian Genome 15, 452-459).

The influence of genetic background and abnormal anxiety-related behavior in serotonin transporter (5-HTT) null mutant mice has been disclosed by Holmes et al (2003, Genes Brain Behav 2:365-380). The mutation was placed on either a B6 congenic or a 129S6 congenic background. B6 congenic 5-HTT null mutants showed increased anxiety like behavior and reduced exploratory locomotion light < -- > dark exploration and elevated plus-maze tests. The 129S6 congenic control mice showed significant

higher anxiety-like behaviors on the light <--> dark exploration and elevated plus-maze tests. The 129S6 congenic 5-HTT null mutant mice exhibited no phenotypic abnormalities on either test. Further, the 129S6 congenic 5-HTT null mutant mice showed reduced 5-HT(1A) receptor binding and reduced 5-HT (1A) receptor function, confirming that 5-HTT null mutation produced alterations in brain 5-HT function in mice on the 129S6 background, and the possibility of the absence of an abnormal anxiety-like phenotype in these mice is due to suppression of the mutation by 129 modifier genes.

Congenic strains are produced to retain phenotypes for complex traits, but often genetically engineered animals do not yield the expected phenotypes (see Doetschman 1999, Laboratory animal Science 49: 137-143). The resulting phenotypic effects are attributed to influence of genetic background. The function of GPR10 gene in mice has been implicated in regulation of the lactation process by mediating prolactin release. The GPR10 knockout mice on a normal diet became hyperphagic and obese (Gu et al 2003, J of Mol Neuroscience 22:93-103).

In real world the mutant congenic rat of the invention cannot be used as model for human depression because in humans the mutation in GPR10 gene has been associated with blood pressure and not obesity and not depression. Taken as a whole, the phenotype of the claimed rat does not correlate with the phenotype of humans that have a mutation in the GPR10 gene.

To date, no teaching is available in the art that establish a predictable association with the mutant GPR10 gene and depression in human.

Relative level of skill of those in the art and quantity of experimentation necessary

Given the lack of guidance in the specification and the unpredictability in the congenic art, it would require a large amount of experimentation to practice the invention as claimed. Neither the art nor the specification provides the skilled artisan with a predictable correlation of GPR10 mutant gene with human depression. To practice the invention as claimed, the skilled artisan would have to perform a large study of individuals suffering with depression and anxiety and matched controls to determine if the human mutant GPR10 exhibits specific phenotypes as disclosed in the invention. Such a study would consist of mainly trial and error analysis, the outcome of which is clearly unpredictable as exemplified by the state of art.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jayanthi Manne whose telephone number is (571) 272-0703. The examiner can normally be reached on Monday - Friday 9:00 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is (703-872-9306).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to telephone number (571)-272-0547.

Jayanthi Manne, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER